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"Recurrent Squamous Cell Carcinoma in a 12 year old boy with Xeroderma Pigmentosum" – Case paper

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ABSTRACT Xeroderma pigmentosum (XP) is a rare autosomal-recessive disorder that appears in early childhood. Patients with XP are highly sensitive to ultraviolet radiation and are prone to develop multiple skin malignancies and can acquire Squamous cell carcinoma (SCC) at an early age. SCC of the skin usually occurs in older patients and commonly develops from preexisting actinic keratosis. SCC is not uncommon in patients with xeroderma pigmentosum and mostly involves the face, head, neck, and scalp.

Here, we present a case of recurrent squamous cell carcinoma of the face in a twelve-year-old boy with xeroderma pigmentosum. Child presented with complaints of maculopapular rashes with ulcerative lesions over the face since the age of nine years. Excisional biopsy of the ulcerative lesion, near nose, was diagnosed as squamous cell carcinoma. Past history also revealed that this lesion was a recurrent one and previously it was diagnosed as squamous cell carcinoma. The challenges of a child with XP who grows up in a sunny environment where the possibility of early onset of squamous cell carcinoma is extremely high in any suspected skin lesion is discussed here.

In sunny areas, proper education to the patient and their parents about ultra-violet light protection and early recognition of any suspicious lesion could be life-saving in XP patients.

KEYWORDS : Xeroderma pigmentosum, Squamous cell carcinoma, malignant tumor, excision biopsy,

Introduction:

Xeroderma pigmentosum (XP) is a rare skin disorder. This is caused by a cellular hypersensitivity to ultraviolet (UV) light as a result of a defect in DNA repair system [1]. XP was first described in 1874 by Hebra and Kaposi. In 1882, Kaposi coined the term xeroderma pigmentosum for this condition, referring to its characteristic dry, pigmented skin [2]. It has been convinced that Xeroderma Pigmentosum (XP) is one of the major risk factors for squamous cell carcinoma (SCC). These malignant tumors mostly involve the face, head, neck, and scalp. We present a case of recurrent SCC of the face, near bridge of the nose in a known case of XP child. Our case illustrates the importance of physician to educate the patient with XP and his family about strict avoidance of sunlight, especially in sunny areas and look for early presentation for any suspicious lesion in skin [3].

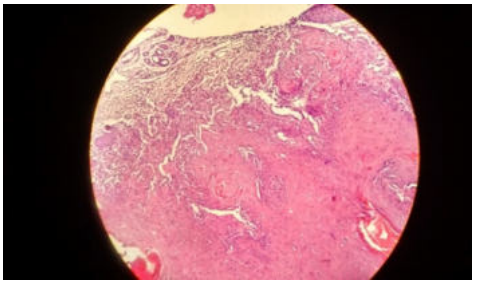
Case Report:

A twelve year old male child, of a known case of XP was brought by his mother to our hospital with history of generalized, multiple, maculopapular rashes, pigmentations, ulcer near nose and skin pigmentation over face, scalp, neck, trunk and photophobia since 2 years. The pigmentation was progressive and more so after exposure to sunlight and over exposed areas. At presentation, he was irritable and photophobic. The skin was unnaturally dry and rough. Initially the lesions were on the face, more marked on both sides of the nose; then the lesions gradually spread all over the body. He experiences intense itching and burning sensation on sun exposure. The child is also suffering from redness of both eyes almost constantly with watering and purulent discharge at frequent intervals for the same duration. There is also marked photophobia. Ulceration on the right side of nose was present for 10 months. Past history revealed similar lesions near nose and was treated for the same at higher center with diagnosis of squamous cell carcinoma. There was no history of seizures or difficulty in hearing. He had a good appetite with normal bowel movements. There was no history of consanguinity in the family. The child was immunized with no significant perinatal history. Development of milestones was normal. The lesions initially started on the face, and spread all over the body. Local examination of ulcer revealed focal ulcero-proliferative lesion on right side of nose measuring 2.1 x 1.5 cm with purulent discharge, focal areas of hemorrhage and everted margins. (Fig 1) Systemic examination including neurological functions was essentially normal.

Haemogram and serum biochemistry was within normal limits. Chest radiography and ultrasonography of abdomen were normal. The ulcero-proliferative lesion near nose was biopsied and the histopathological diagnosis of well differentiated squamous cell carcinoma was made. (Fig 2). The tissue was lined by dysplastic stratified squamous epithelium showing severe dysplasia. The basement membrane was interrupted and tumor cells were seen in the sub-epithelium. These cells were arranged diffusely in nest, and in cords. The tumor cells were moderately pleomorphic with abundant glassy and eosinophilic, cytoplasm and central round to oval vesicular nuclei with prominent nucleoli (Fig3). Atypical dyskeratotic cells and keratin pearls were also seen. Moderate inflammation was seen in the stroma (Fig4).

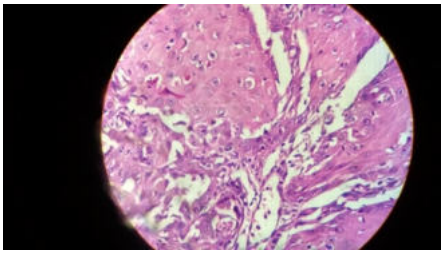
Ulcero-proliferative lesion on right side of nose (Fig1).

Biopsy showing features of well differentiated squamous cell carcinoma (Fig2).

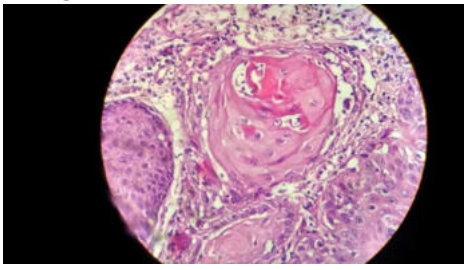


Moderately pleomorphic tumor cells with abundant glassy and

eosinophilic cytoplasm (Fig 3).



Atypical dyskeratotic tumor cells with early keratin pearl formation (Fig 4).



Discussion:

XP is a rare (1 case/500,000 newborns), recessively transmitted genetic disease. It has been reported in all races, including the Blacks despite the protective nature of skin pigmentation found in this race. It affects both males and females in approximately equal proportions. Consanguinity or first cousin relationships between parents of affected children has been found in 30% of cases [4]. XP is seen either in infancy or early childhood especially around the age of two [5]. At birth, these patients are usually normal, but within the first 2 years they start developing changes in the skin on sun-exposed areas: progressive irregular freckling, mottled hyperpigmentation and hypopigmentation, dryness, atrophy and telangiectases. These are similar to those observed in older individuals with light-complexioned skin and chronic sun exposure [6].

XP is characterized by a heightened reaction to sunlight (photosensitivity) with skin blistering occurring after exposure to the sun. In some cases, pain and blistering may occur immediately after contact with sunlight. Acute sunburn and persistent redness or inflammation of the skin (erythema) are also early symptoms of XP. In most cases, these symptoms may be apparent immediately after birth or occur within the next three years. In other cases, symptoms may not develop until later in childhood or, more rarely, may not be recognized until adulthood. Other symptoms of XP may include discolorations, weakness and fragility, and/or scarring of the skin. XP affects the eyes as well as the skin and has been associated with several forms of skin cancer. In some cases, XP may occur along with dwarfism, mental retardation, and/or delayed development [7].

The basic defect in XP is in the nucleotide excision repair (NER), leading to deficient repair of DNA damaged by UV radiation. This intensively studied process consists of the removal and replacement of damaged DNA with new DNA. Two types of NER exist, global genome (GG-NER) and transcription coupled (TC-NER). The last decade has seen the cloning of the key elements of NER, and the process has been reconstituted in vitro. Several subtypes of XP (i.e., XP complementation groups) have been identified, based upon different defects in the body's ability to repair DNA damaged by ultraviolet light (UV). According to the medical literature, the symptoms and findings associated with the classic form of xeroderma pigmentosum, known as XP type A (XPA), may also occur in association with the other XP subtypes. These include: XP type B (XPB); XP type C (XPC); XP type D (XPD); XP type E (XPE); XP type F (XPF); and XP type G (XPG). These XP subtypes are transmitted as an autosomal recessive trait. In addition, another subtype of the disorder, known as XP, dominant type, has autosomal dominant inheritance. In addition to the XP subtypes discussed above, researchers have identified another form of the disorder known as XP, variant type (XP-V). As with the other XP subtypes, symptoms and findings associated with the classic form of XP may also be seen in individuals with XP-V. XP-V cells have a normal or near normal ability to repair UV-induced DNA damage (nucleotide excisional repair); however, they are defective in replicating UV-damaged DNA during the division and reproduction of cells. Although the disorder's mode of inheritance is unknown, most researchers suspect that XP-V is transmitted as an autosomal recessive trait [8].

There are very few reports of other types of cutaneous neoplasms including angioma or fibrosarcoma. Additionally, there is a 10- to 20-fold increase in the frequency of occurrence of lung, uterine and CNS neoplasms in patients with XP. Anterior tongue neoplasms have been reported and are presumably due to direct exposure to the sun [9].

The clinical course of the disease can be divided into three stages. The skin is healthy at birth. Typically, the first stage makes its appearance after the age of six months. This stage is characterized by diffuse erythema, scaling and freckle-like areas of increased pigmentation in sun-exposed areas, with initial involvement of the face. With progression of the disease, the skin changes appear on the lower legs, neck and arms. While these features tend to diminish during the winter months with decreased sun exposure in the initial stage of the disease, they become permanent as time passes. The second stage is characterized by poikiloderma, which consists of skin atrophy, telangiectasias and mottled hyper and hypo pigmentation. The third stage is heralded by the appearance of numerous malignancies, including squamous cell carcinomas, malignant melanomas, basal cell carcinomas and fibrosarcomas. These malignancies may occur as early as at 4-5 years of age, and are more prevalent in sun-exposed areas [10].

Ocular problems occur in nearly 80% of individuals with XP. The initial problems begin with photophobia and conjunctivitis. Eyelid solar lentigenes occur in the first decade of life and may transform later into malignant melanomas. Other ocular findings include ectropion, symblepharon with ulceration, repeated conjunctival inflammations, infections and scarring. In addition, vascular pterigia, fibrovascular pannus of the cornea and epitheliomas of the lids, the conjunctiva and the cornea can occur. Finally, the propensity for malignancies, such as squamous cell carcinomas, basal cell carcinoma, sebaceous cell carcinomas and fibrosarcomas can also involve the eye of the patient with XP. In our case also, the child had recurrent, well differentiated squamous cell carcinoma near the right side of nose. Neurologic problems are seen in nearly 20% of patients with XP, more commonly in groups XPA and XPD. The severity of these problems is proportional to the sensitivity of XP fibroblasts to UV radiation. Other problems include microcephaly, spasticity, hypo or areflexia, ataxia, chorea, motor neuron signs, sensorineural deafness, supranuclear ophthalmoplegia and mental retardation. The neurologic problems might overshadow the cutaneous manifestations in some patients with XP. De Sanctis- Cacchione syndrome refers to the combination of XP and neurological abnormalities including mental retardation and cerebellar ataxia, hypogonadism and dwarfism. Fortunately, none of the above mentioned neurological problems were seen in our patient. A few studies have also shown a co-relation between the risk of primary lung cancer and polymorphism of the DNA repair gene, especially among smokers in group A and group G of XP [11].

No consistent routine lab abnormalities are present in XP. The diagnosis is based mostly on clinical findings and biopsy analysis. However, many studies can be performed in specialized laboratories to help in diagnosing the condition. These studies include cellular hypersensitivity to UV radiation, chromosomal breakage studies, complementation gene sequencing to identify the specific gene complementation group. Antenatal diagnosis is possible by amniocentesis or chorionic villi sampling. A faster technique is the alkaline comet assay (single cell gel electrophoresis assay) [12].

Sometimes, electroencephalographic findings may also be abnormal. In our case, however, the diagnosis was made on the basis of history, clinical features and the histopathological reports on the lesion. Malignant melanomas and squamous cell carcinomas are the two most important causes of mortality in patients with XP. Patients younger than twenty years have a thousand fold higher incidence of non-melanoma skin cancer and melanomas. Actinic damage occurs in XP patients by age of one to two years. Although XP is ultimately fatal, life can be prolonged by paying strict attention to simple preventive measures to minimize sun exposure. The aim of the treatment is to educate the patient regarding these measures, to provide regular check ups with a dermatologist and to detect and treat early any malignancies that may occur. The use of sunscreens in conjunction with other sun-avoidance methods e.g. protective hats, eyewear etc. can minimize UV induced damage in patients with XP. Oral retinoids have been shown to decrease the incidence of skin cancer in patients with XP, but the therapy is limited by dose-related irreversible calcification of ligaments and tendons [13].

Environmental factors also appear to cause DNA damage and abnormal repair, the most important of which is ultraviolet radiation (UVR). UVR induces damage in DNA strands to form photoproducts that result when adjacent pyrimidine molecules fuse together to produce covalently linked thymine dimers. These must be excised and replaced if accurate DNA synthesis and replication is to occur. Ultraviolet radiation produces damage to the DNA, which provides an opportunity for mutant malignant growth. All forms of cutaneous malignancies may develop in the exposed areas and death occurs in early adulthood because of metastatic disease [14].

Early detection of these malignancies is necessary because they are fast-growing, metastasize early and lead to death: most patients with XP do not live beyond the third decade because of development of tumor. Surgical excision of the tumors and grafting of skin from non-light-exposed areas is the first line of treatment. Chemo- and radiotherapy have been tried, however, no effective treatment has been found [15].

Since the underlying genetic defect cannot yet be corrected, prophylactic measures are of utmost importance. Children with XP should be protected from exposure to sun. Whenever possible, this is done by having the patients to wear protective clothing, applying sunscreens and using sunglasses with side shield. Genetic counselling of affected families is of importance. Amniocentesis for prenatal diagnosis of XP and interruption of the pregnancy may be discussed [16].

Conclusion: XP is a rare genetic disease characterized by defective DNA repair leading to clinical and cellular hypersensitivity to ultraviolet radiation. Clinicians should be aware of the possibility of early onset of SCC and other cutaneous neoplasms, when young patients with XP present with any skin lesion. Proper education to the parents about the importance of strict UV light protection, especially in sunny areas, is warranted. Early recognition of any suspicious lesion, diagnosis and management may be life-saving. Genetic counseling should be offered for families at risk. Follow-up care should be geared to educate the patient and the patient's parents about effective sun protection and early recognition of skin cancer. Prognosis is poor with less than 40% of those affected by cutaneous malignancies, surviving beyond the second decade.

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